[COMMENTARY]

Fulminans in Dermatology: A Call to Action

A Recommendation for Consideration of the Term *Scleredema Fulminans*

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ABSTRACT

The term *fulminans* is used infrequently in dermatology, being reserved for those cases of rapid onset with potentially severe sequelae or those that are life-threatening, thereby warranting urgent intervention. In this commentary, the authors propose that the term *scleredema fulminans* be utilized in severe, progressive cases of scleredema adultorum of Buschke presenting with rapid onset. (*J Clin Aesthet Dermatol.* 2014;7(6):42–45.)

Acne fulminans, rosacea fulminans, and purpura fulminans are all urgent conditions that command immediate attention and treatment to prevent severe sequelae; the corresponding diagnoses of acne vulgaris, rosacea, and purpura (some variants) can be approached deliberately. The authors propose that the term *fulminans* be applied to another dermatological disorder—scleredema—when the presentation is rapid, aggressive, and life-threatening. The case that prompted this commentary has been published by the authors' rheumatological colleagues at their institution as "Scleredema in a Patient with AIDS-related Lipodystrophy Syndrome."[1] The following is a summary of the case.

A 43-year-old man presented with a three-month history of abrupt-onset, progressive neck, shoulder, and upper back swelling. His symptoms began when he was diagnosed with new-onset type-2 diabetes mellitus and started on insulin. Accompanying the skin changes, were worsening cough and shortness of breath resulting in considerable dyspnea. Curiously, he noted dysphonia resulting in a "Kermit-the-frog-like" voice. During this time he reported a 30-pound weight gain, worsening blood sugar control, and increasing hypertension. His history was also significant for coronary artery disease, hypertension, dyslipidemia, and an 11-year history of human immunodeficiency virus (HIV) controlled by antiretroviral therapy.

On exam, he exhibited facial plethora with erythema. A prominent buffalo hump was present on the upper back with increased neck girth (Figure 1). Symmetric, firm, non-pitting induration of his shoulders and back gave the appearance of a "shield-shaped" trunk and resulted in limited and painful range of motion (Figure 2). The lower extremities and distal upper extremities were uninvolved.

Laboratory studies revealed an absolute CD4+ T-cell count of 479 cells/µL with an undetectable HIV ribonucleic acid viral load. A complete blood count, complete metabolic panel, thyroid function testing, creatinine kinase, and troponin-T levels were unremarkable except for an elevated blood glucose (251mg/dL) and hemoglobin A1c of 8.7 percent (reference <5.7%), reflecting his poorly controlled diabetes. Serum and urine protein electrophoresis were negative for monoclonal paraprotein. Immunoglobulin A (IgA) levels were within normal limits. Antistreptolysin O titer was also negative.

Imaging of the neck demonstrated excessive subcutaneous fat in the absence of lymphadenopathy or cellulitis. An echocardiogram was obtained and compared to a prior echocardiogram. It demonstrated new wall motion abnormalities including mild hypokinesis of the left ventricular anterior and anteroseptal walls with a reduction of left ventricular ejection fraction from 60–65 percent to 50 percent. New borderline concentric left

DISCLOSURE: The authors report no relevant conflicts of interest.
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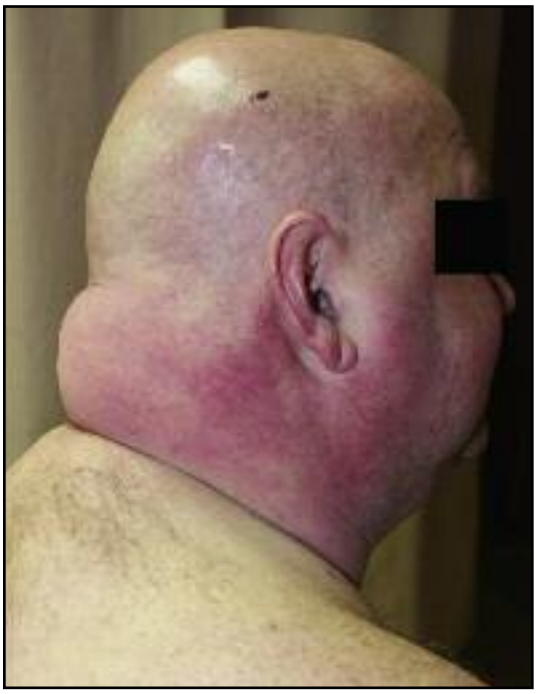

Figure 1. Firm, non-pitting induration of the posterior neck and upper back

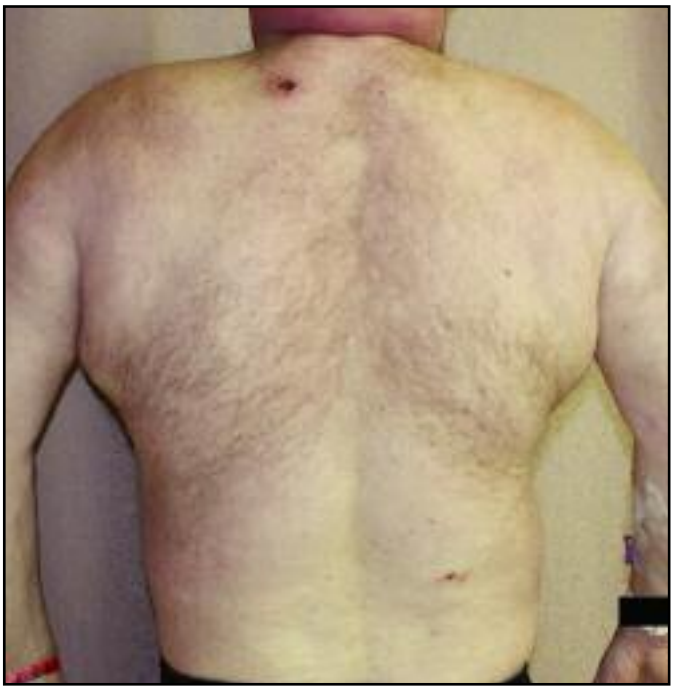

Figure 2. Symmetric, firm, non-pitting induration of the chest, shoulders, and upper back giving the appearance of a "shield-shaped" trunk. The site of a deep-wedge biopsy is seen on the left upper back.

ventricular hypertrophy was noted with impaired diastolic relaxation. Pulmonary function testing revealed mild obstructive disease with air trapping and moderately reduced diffusion capacity.

A deep wedge biopsy of the upper back revealed coarse collagen bundles extending into the subcutaneous fat with preservation of the skin appendages. A colloidal iron stain demonstrated the presence of acid mucopolysaccharides between the collagen clefts, confirming the diagnosis of scleredema adultorum of Buschke (Figure 3).

Due to the rapid progression of symptoms with apparent cardiac and pulmonary compromise, coupled with the lack of suitable alternative therapy given the patient's comorbidities, the decision was made to initiate intravenous immunoglobulin (IVIG) therapy. The patient received a total treatment dose of 2g/kg over four days. He tolerated the infusions well and underwent subsequent infusions on a monthly basis.

The authors evaluated the patient in their office 28 days after his initial infusion of IVIG. He reported marked improvement in his dyspnea and a softening in the previously indurated skin of his neck, shoulders, and upper back. His dysphonia was improving with a return to his "normal voice." A repeat echocardiogram was performed after three monthly infusions of IVIG. Despite clinical improvement, the echocardiogram remained unchanged.

Scleredema adultorum of Buschke (SAB) is an infrequent disorder characterized by mucin deposition in the reticular dermis. Its classic description has been credited to Dr. Abraham Buschke who characterized the development of a hardness of the skin in a 44-year-old man following influenza infection in 1902.[2] A relationship to diabetes mellitus was established in 1970 and the term "scleredema diabeticorum" is often used in this setting.[3,4]

Three clinical variants of SAB have since been detailed.[5,6] Type I is the classic type described by Buschke. In this group, a febrile prodrome with malaise and an acute respiratory infection (most commonly streptococcal) is followed by the sudden development of firm induration of the skin over the posterior neck that spreads upward to the head and face and downward over the trunk and proximal upper extremities. The tongue and pharynx may be involved leading to difficulty opening the mouth and swallowing. Most cases completely resolve without intervention in six months to two years. Type 2 SAB shares similar clinical features to Type 1; however, Type 2 has an insidious onset without the preceding febrile illness. It may persist for years and is frequently associated with a monoclonal gammopathy. Type 3 is seen in middle-aged obese individuals, more often in men, with insulin-dependent diabetes mellitus and is referred to as scleredema diabeticorum. The onset is subtle with a slowly progressive, usually nonresolving scleredema refractory to treatment. Complications of diabetes tend to be the cause of mortality before skin involvement becomes widespread. In addition, there have been case reports of scleredema associated with pituitary-adrenocortical neoplasms,[7] carcinoid syndrome,[8] carcinoma of the gall bladder,[9] and HIV infection.[1,10]

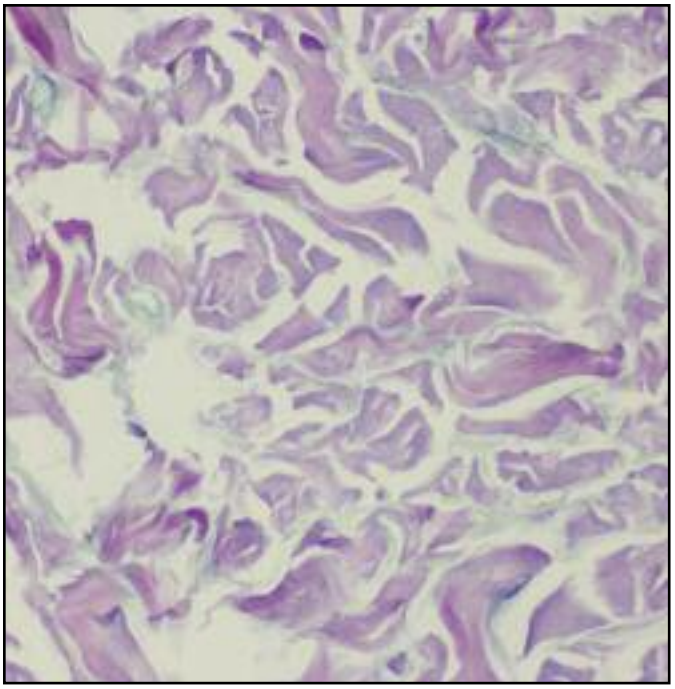

Figure 3. Mucin deposition is readily apparent between collagen bundles (colloidal iron, original magnification 400x).

While classically thought to be a benign mucinosis, systemic involvement has been observed and may warrant additional investigation. Cardiac involvement including friction rub, gallop, arrhythmia, ST segment elevation, inverted T-waves, and right-sided heart failure have been reported.[11,12] A post-mortem cardiac biopsy in one female with long-standing scleredema and multiple myeloma who subsequently developed right-sided heart failure demonstrated mucopolysaccharide deposition between the cardiac muscle bundles.[13] Pulmonary fibrosis and pleural effusions have also been shown to correlate with cutaneous disease.[11]

No single therapy has been consistently effective for treatment of scleredema; however, there have been case reports of successful treatment with psoralen + ultraviolet A (PUVA),[14] UVA1,[15,16] narrowband UVB,[17] cyclosporine,[18] allopurinol,[19] high-dose penicillin,[20] localized electron beam therapy,[21,22] and IVIG.[23,24] Treatment with methotrexate and systemic corticosteroids has been disappointing.[25,26, 27] Our patient was experiencing worsening dyspnea and functional disability requiring immediate therapeutic intervention. Given his concurrent comorbidities (diabetes, HIV, and dyslipidemia) and progressive symptoms warranting urgent reversal of mucinosis, IVIG therapy was determined to be the best option.

IVIG therapy has been used since the 1950s to treat primary immunodeficiency diseases. Expanding upon its initial indication as antibody replacement, IVIG has proven useful in a number of autoimmune and inflammatory diseases, such as Kawasaki's disease, graft-versus-host disease, Guillain-Barré syndrome, myasthenia gravis, pemphigus vulgaris, bullous pemphigoid, epidermolysis bullosa acquisita, and Stevens-Johnson syndrome or toxic epidermal necrolysis. Various anti-inflammatory and immunomodulatory effects have been attributed to the IgG molecule. These effects are largely mediated by the Fab and Fc portion of IgG and include suppression or neutralization of autoantibodies and cytokines, neutralization of activated complement components, blockade of leukocyte-adhesion-molecule binding, blockade of FcRn to shorten autoantibody half-life, and blockade of proinflammatory FcγR.[28] When used for the treatment of autoimmune and inflammatory disease, IVIG doses four to fives times higher than those needed for antibody replacement of primary immunodeficiency are required. Most often this is administered as 2g of IVIG per kilogram of body weight given over a period of two to five days on a monthly basis. At this dose, Aichelburg et al[24] achieved clinical response in a case of rapidly progressing post-streptococcal SAB within 10 days following the initial infusion of IVIG. Of note, patients with selective IgA deficiency are at an increased risk of anaphylaxis from blood products containing IgA (including IVIG) due to circulating anti-IgA antibodies. IgA levels were verified as normal in our patient and he tolerated IVIG well with significant clinical improvement of mucinosis during follow up.

While it can be argued that the authors' patient simply had a severe case of scleredema diabeticorum, utilizing the adjective *fulminans* clearly warns of the aggressive, potentially life-threatening nature of the disorder warranting immediate therapy. It is plausible that a synergistic effect in the setting of HIV with new-onset and poorly controlled diabetes contributed to the dramatic onset of disease in the authors' patient. Inevitably, there will be other such cases and having the appellation *scleredema fulminans* in the literature would be most helpful to the clinician in securing such treatment as IVIG for these patients. This distinction is important—just as a clinician might utilize topical agents in managing acne vulgaris, the approach taken with acne fulminans mandates systemic treatment (i.e., isotretinoin, dapsone, or prednisone). The authors would encourage dermatologists to use the term *scleredema fulminans* in cases similar to our patient, as it may prove to be lifesaving.

REFERENCES

1. Yachoui R, Traisak P, Jagga S. Scleredema in a atient with AIDS-related lipodystrophy syndrome. *Case Rep Endocrinol.* 2013;2013:943798. Epub 2013 Jan 10.
2. Sweitzer SE, Laymon CW. Scleredema adultorum (Buschke). *Arch Dermatol.* 1938;37(3):420–430.
3. Fleischmajer R, Faludi G, Krol S. Scleredema and diabetes mellitus. *Arch Dermatol.* 1970;101(1):21–26.
4. Cohn BA, Wheeler CE, Briggaman RA. Scleredema adultorum of Buschke and diabetes mellitus. *Arch Dermatol.* 1970;101(1): 27–35.
5. Graff R. Discussion of scleredema adultorum. *Arch Dermatol.* 1968;98:319–320.
6. Beers WH, Ince A, Moore TL. Scleredema adultorum of Buschke:

a case report and review of the literature. *Semin Arthritis Rheum.* 2006;35(6):355–359.
7. Oyama N, Togashi A, Kaneko F, Yamamoto T. Two cases of scleredema with pituitary-adrenocortical neoplasms: an underrecognized skin complication. *J Dermatol.* 2012;39(2): 193–195.
8. Yu JI, Park W, Lee KK, Park W. Scleredema adultorum of Buschke associated with a carcinoid tumor. *Int J Dermatol.* 2009;48(7):784–786.
9. Manchanda Y, Das S, Sharma VK, Srivastava DN. Scleredema associated with carcinoma of the gall bladder. *Br J Dermatol.* 2005;152(6):1373–1374.
10. Rongioletti F, Ghigliotti G, De Marchi R, Rebora A. Cutaneous mucinoses and HIV infection. *Br J Dermatol.* 1998;139(6): 1077–1080.
11. Curtis AC, Shulak BM. Scleredema adultorum. Not always a benign self-limited disease. *Arch Dermatol.* 1965;92(5):526–541.
12. Isaac A, Costa I, Leal I. Scleredema of Buschke in a child with cardiac involvement. *Pediatr Dermatol.* 2010;27(3):315–317.
13. Rimon D, Lurie M, Storch S, et al. Cardiomyopathy and multiple myeloma. Complications of scleredema adultorum. *Arch Intern Med.* 1988;148(3):551–553.
14. Nakajima K, Iwagaki M, Ikeda M, Kodama H. Two cases of diabetic scleredema that responded to PUVA therapy. *J Dermatol.* 2006;33(11):820–822.
15. Thumpimukvatana N, Wongpraparut C, Lim HW. Scleredema diabeticorum successfully treated with ultraviolet A1 phototherapy. *J Dermatol.* 2010;37(12):1036–1039.
16. Kroft EB, de Jong EM. Scleredema diabeticorum case series: successful treatment with UV-A1. *Arch Dermatol.* 2008;144(7): 947–948.
17. Xiao T, Yang ZH, He CD, Chen HD. Scleredema adultorum treated with narrow-band ultraviolet B phototherapy. *J Dermatol.* 2007;34(4):270–272.
18. Mattheou-Vakali G, Ioannides D, Thomas T, et al. Cyclosporine in scleredema. *J Am Acad Dermatol.* 1996;35(6):990–991.
19. Lee FY, Chiu HY, Chiu HC. Treatment of acquired reactive perforating collagenosis with allopurinol incidentally improves scleredema diabeticorum. *J Am Acad Dermatol.* 2011;65(4): e115–e117.
20. Krasagakis K, Hettmannsperger U, Trautmann C, et al. Persistent scleredema of Buschke in a diabetic: improvement with high-dose penicillin. *Br J Dermatol.* 1996;134(3):597–598.
21. Tamburin LM, Pena JR, Meredith R, Soong VY. Scleredema of Buschke successfully treated with electron beam therapy. *Arch Dermatol.* 1998;134(4):419–422.
22. Angeli-Besson C, Koeppel MC, Jacquet P, et al. Electron-beam therapy in scleredema adultorum with associated monoclonal hypergammaglobulinaemia. *Br J Dermatol.* 1994;130(3): 394–397.
23. Barde C, Masouyé I, Saurat JH, Le Gal FA. Scleroedema adultorum Buschke in a diabetic subject: intravenous immunoglobulin therapy. *Ann Dermatol Venereol.* 2009;136(4): 360–363.
24. Aichelburg MC, Loewe R, Schicher N, et al. Successful treatment of poststreptococcal scleredema adultorum Buschke with intravenous immunoglobulins. *Arch Dermatol.* 2012;148(10): 1126–1128.
25. Seyger MM, van den Hoogen FH, de Mare S, et al. A patient with a severe scleroedema diabeticorum, partially responding to low-dose methotrexate. *Dermatology.* 1999;198(2):177–179.
26. Breuckmann F, Appelhans C, Harati A, et al. Failure of low-dose methotrexate in the treatment of scleredema diabeticorum in seven cases. *Dermatology*. 2005;211(3):299–301.
27. Kurtoglu S, Yüksel S, Gündüz Z, et al. Use of high-dose intravenous corticosteroid treatment in a child with scleredema. *J Emerg Med.* 2004;26(2):245–246.
28. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med.* 2012;367(21): 2015–2025.